

## **REMARKS**

This application is a National Stage Application filed under 35 U.S.C. § 371 based on International Application No. PCT/US04/3697, filed November 4, 2004, which claims priority to U.S. Provisional Application Serial No. 60/517,495, filed November 4, 2003, the entire contents each of which are incorporated herein by reference. Applicants have amended page 1 of the specification to reflect the above related application information.

Claims 1-25 were pending before the Office. By this Amendment, claims 1, 3, 15, 16, 19 and 21 are hereby amended. Claims 2, 5, 7-14, 17, 20, 23 and 25 are hereby cancelled. No claims are added. Applicants reserve the right to pursue any cancelled claims in one or more continuing applications. Thus, by entry of this Amendment, claims 1, 3, 4, 6, 15, 16, 18, 19, 21, 22 and 24 will be pending before the Office.

No new matter is added by these amendments.

The amendments made herein have been made solely to claim more fully the invention and/or to expedite prosecution of the present application and should not necessarily be construed as an acquiescence to any of the Examiner's rejections in the Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed or similar claims in one or more subsequent applications. Support for the amendments can be found throughout the originally-filed application, including the specification, drawings, examples and claims.

### **The rejection under 35 U.S.C. 112, second paragraph, is overcome**

The Office action rejects claim 20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the

invention. While the Applicants do not necessarily agree with the rejection, claim 20 has been cancelled in favor of incorporation of its terms into base claim 19. Accordingly, the rejection of claim 20 is overcome.

Applicants respectfully request reconsideration and withdrawal of the rejection.

**The rejections under 35 U.S.C. 102 are overcome**

The Office action rejects claim 25 under 35 U.S.C. 102(b) as allegedly being anticipated by Zhang et al. (Journal of Biological Chemistry, Oct. 18, 2002, Vol. 272, pp. 39379-39387) (“Zhang”).

Claims 1, 3-19 and 21-24 stand rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Bacus et al. (U.S. Published Application No. 2003/0045451) (“Bacus”).

Claims 1-3, 7, 8, 12, 13, 15, 16, 19-21 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by the abstract of Hedley et al. (Clinical Cancer Research, November 2001, Vol. 7, No. 11, suppl., pp. 3712S) (“Hedley”).

The Office action rejects claims 1, 4-7, 9-12, 14, 15, 17-19 and 22-24 under 35 U.S.C. 102(e) as allegedly being anticipated by Taylor et al. (WO 2005/032495) (“Taylor”).

Claims 1, 2, 4-6, 15, 17 and 18 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Eveleigh et al. (U.S. Published Application No. 2004/0121375) (“Eveleigh”).

Applicants respectfully disagree with each of the rejections and traverse as follows.

As an initial matter, claims 2, 5, 7-14, 17, 20, 23 and 25 are cancelled by this Amendment. Thus, the preceding rejections are moot to the extent that they apply to the cancelled claims. In particular, the rejection over Zhang is necessarily now overcome as claim 25 is now cancelled. The remaining rejections are traversed as follows.

The Examiner is respectfully referred to M.P.E.P § 2131 which states that “[a] claim is anticipated *only if each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” See *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). As shown below, none of the references expressly or inherently teach each and every element of the claimed invention, and thus, do not anticipate the present claims.

Turning first to the presently claimed invention, the claims are drawn generally to diagnostic methods for evaluating Raf kinase inhibitors by measuring the level of expression of one or more protein markers, e.g., pERK, using immunohistochemical methods. For example, the invention as defined by claim 1 is directed to a method to monitor the response of a patient being treated for cancer by administering a Raf kinase inhibitor, comprising the steps of: (a) determining the level of expression of one or more proteins in a first biological sample taken from the patient prior to treatment with the Raf kinase inhibitor; (b) determining the level of expression of the one or more proteins in at least a second biological sample taken from the patient subsequent to the treatment with the Raf kinase inhibitor; and (c) comparing the level of expression of the one or more proteins in the second biological sample with the level of expression of the one or more proteins in the first biological sample; wherein the level of protein expression is assessed by immunohistochemistry and wherein a change in the level of expression of the one or more proteins in the second biological sample compared to the level of expression of the one or more proteins in the first biological sample indicates the efficacy of the treatment with the Raf kinase inhibitor. The one or more proteins can include pERK as a protein marker for evaluating the efficacy of the Raf kinase inhibitor function.

Bacus relates to methods for detecting the expression and/or activation of proteins and ligands that are involved in the activation of the tumor-related signal transduction protein, AKT, or the inducing of the expression of the gene encoding AKT [an angiogenesis-inhibiting product]. The specification states that the “invention specifically provides methods for quantitatively determining expression and activation levels for cellular proteins encoded by c-kit, SCF and AKT, in tumor cells, including human tumor cells, as detected in cell or tissue sample from an individual.” In addition, the reference proposes monitoring the expression and/or activation levels of the tumor markers c-kit, SCF and AKT in connection with the administration of inhibitors of same as a measure of the utility of such compounds against those tumor markers.

Contrary to the present invention, however, Bacus does not teach or suggest any method of testing a Raf kinase inhibitor or treatment therewith in a patient having cancer by the evaluation of the activity or expression level of one or more marker proteins, such as pERK, whose activity or expression level is tied to Raf activity. As such, Bacus fails to teach each and every element of the claim, and thus, does not anticipate the claims. Reconsideration and withdrawal of the rejection over Bacus is respectfully requested.

Hedley relates to a flow-cytometry-based assay to measure the activation of ERK1 and ERK2 in peripheral blood T-lymphocytes as a consequence of administering a Raf kinase inhibitor. Unlike the present invention, however, Hedley does not concern itself with cancer tissue, but rather is focused on measuring the effects of ERK1 and ERK2 activation levels in peripheral blood T-lymphocytes. Moreover, Hedley does not have anything to do with the use of immunohistochemical methods for detecting the expression and/or activity levels of pERK, which is a requirement of each of the claims of the present invention. According, Hedley does

not teach each and every claim element of the present invention. Reconsideration and withdrawal of the rejection over Hedley are respectfully requested.

Taylor relates to gene expression profiles, microarrays and methods for using same for evaluating and diagnosing lung cancer. Taylor does not teach or suggest any diagnostic method for evaluating Raf kinase inhibitors by measuring the level of expression of one or more protein markers, e.g., pERK, using immunohistochemical methods. Since Taylor does not teach each and every claim element of the presently amended claims, Taylor does not anticipate the claims.

Even assuming, *arguendo*, that the present invention were obvious over Taylor, the Applicants would benefit from the exclusion under 35 U.S.C. 103(c) since the subject matter of Taylor and “the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.” 35 U.S.C. 103(c).

More in particular, both Taylor and the instant patent application were each separately assigned to Bayer Pharmaceuticals Corporation. The assignment of Taylor (against the corresponding U.S. Published Application No. 2006/240441) is recorded at Reel/Frame 017178/0570. The assignment of the present invention (against the published application, US 2007/0292887) is recorded at Reel/Frame 017469/0854.

Moreover, the inventors of both Taylor and of the present invention would have been obligated to assign their right, title and interest in their respective inventions to Bayer Pharmaceuticals Corporation at the time of the present invention given the requirements of their employment contracts with the company. Because the conditions of Section 103(c) can be met, the present invention cannot be rendered obvious over Taylor. Accordingly, reconsideration and withdrawal of the rejection in view of Taylor are respectfully requested.

Eveleigh relates to the use of adrenomedullin as a biomarker for evaluating Raf kinase inhibitors through the use of gene expression profiling and other related molecular tests. Eveleigh does not teach or suggest a diagnostic method for evaluating Raf kinase inhibitors by measuring the level of expression of one or more protein markers, including especially, pERK, using immunohistochemical methods. Since Eveleigh does not teach each and every claim element of the presently amended claims, Eveleigh does not anticipate the claims.

Even assuming, *arguendo*, that the present invention were obvious over Eveleigh, the Applicants would benefit from the exclusion under 35 U.S.C. 103(c) since the subject matter of Eveleigh and “the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.” 35 U.S.C. 103(c).

More in particular, both Eveleigh and the instant patent application were each separately assigned to Bayer Pharmaceuticals Corporation. The assignment of Eveleigh is recorded at Reel/Frame 014375/0623. The assignment of the present invention (against the published application, US 2007/0292887) is recorded at Reel/Frame 017469/0854.

Moreover, the inventors of both Eveleigh and of the present invention would have been obligated to assign their right, title and interest in their respective inventions to Bayer Pharmaceuticals Corporation at the time of the present invention given the requirements of their employment contracts with the company. Because the conditions of Section 103(c) can be met, the present invention cannot be rendered obvious over Eveleigh. Accordingly, reconsideration and withdrawal of the rejection in view of Eveleigh are respectfully requested.

In view of at least the comments above, Applicants respectfully request reconsideration and withdrawal of each of the Section 102 rejections.

**The obviousness-type double-patenting rejections are requested to be held in abeyance**

The Office action provisionally rejects claims 1, 7, 12, 15 and 19 as being unpatentable over claims 1, 2, 4-6, 8-10, 12, 13 and 15 of copending Application No. 10/581,213. In addition, claims 1, 2, 4, 6, 15 and 18 are provisionally rejected over claims 1-18 of copending Application No. 11/589,295. Further, claims 1, 2, 4, 6, 7, 9, 11, 12, 15, 18, 19, 20, 22 and 24 are provisional rejected over claims 1, 3, 5-7, 27 and 28-50 of copending Application No. 11/589,824. Still further, claims 1, 2, 4, 6, 15 and 18 are provisionally rejected over claims 1, 3, 5-7, 27, 28-50 of copending Application No. 10/675,406.

It remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable; hence any statement regarding this rejection made on Applicants' part would be premature. Therefore, Applicants respectfully traverse this rejection, and request that this rejection should be held in abeyance until subject matter is deemed allowable in this application. Applicants will consider filing Terminal Disclaimers, if necessary, to overcome any remaining rejections at the time allowable subject matter is known.

## **CONCLUSION**

In view of the remarks herein, Applicants respectfully request reconsideration and withdrawal of all of the rejections as Applicants believe the application to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Dated: November 14, 2008

Respectfully submitted,

By: /Gabriel J. McCool/

Gabriel J. McCool, Reg. No. 58,423  
EDWARDS ANGELL PALMER & DODGE LLP  
P.O. Box 55874  
Boston, Massachusetts 02205  
(203) 975-7505